Oral antimicrobial peptides

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Review

Oral Antimicrobial Peptides: Types and Role in the Oral Cavity

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Oral Antimicrobial Peptides: Types and Role in the Oral Cavity

Abstract

Antimicrobial peptides (AMPs) are a wide-ranging class of host-defense molecules that act early to contest against microbial invasion and challenge. These are small cationic peptides that play an important in the development of innate immunity. In the oral cavity, the AMPs are produced by the salivary glands and the oral epithelium and serve defensive purposes. The aim of this review is to discuss the types and functions of oral AMPs and their role in combating microorganisms and infections in the oral cavity.

Keywords: Antimicrobial peptides (AMPs); oral cavity; defensins; cathelicidins; histatins; dental applications.

Contents

1. Introduction

All living organisms have defence systems for combating microorganisms and potential pathogens (Zasloff 2002, Dale, Tao et al. 2006, Cardot Martin, Michel et al. 2015). In the higher vertebrates, prior to the evolution of adaptive immunity, a more simpler and nonspecific system of innate immunity evolved and still continues to play a role as the principal defence system for almost all living organisms (Adonogianaki, Moughal et al. 1993, Adonogianaki, Mooney et al. 1996, Aguilera, Andres et al. 1998). The innate immunity modulates its antimicrobial functionality by small cationic peptides with activity against gram-positive and negative bacteria, parasites, fungi and some viruses (Akalin, Bulut et al. 1993, Allaker, Zihni et al. 1999, Allgrove, Gomes et al. 2008). The mechanism of action against microbes and pathogens is principally attributed to the disruption of the microbial cell membrane (van 't Hof, Veerman et al. 2001, Shai 2002). However, complete understanding of the exact process or processes is deficient and it is plausible that other mechanisms are at play which are yet to be identified (Quinones-Mateu, Lederman et al. 2003, Sinha, Cheshenko et al. 2003, Wang, Owen et al. 2004, Yasin, Wang et al. 2004, Gordon, Huang et al. 2005).

The innate immune system augments the physical and chemical barriers e.g. skin and mucous membranes by producing antimicrobial peptides (AMPs) (Hancock and Sahl 2006). AMPs have a widespread distribution in human body and have antimicrobial activity against microorganisms (Zasloff 2002, Gordon, Romanowski et al. 2005). All AMPs are extracted from larger precursors and comprise of a signal sequence with post-translational modification that includes glycosylation (Sewald and Jakubke 2002), proteolysis (Vos, Kuipers et al. 1995), amino-acids isomerization, carboxy-terminal amidation and halogenation (Bulet, Dimarcq et al. 1993). To date around 106 Human host defense peptides have been identified

(Wang 2014). AMPs are found in oral saliva, in the epithelium and in neutrophils (Dale, Tao et al. 2006). AMPs are classified in different classes according to amino acid composition, size and conformational structures (Table-1) (Hancock and Lehrer 1998, Brogden 2005, Harris, Dennison et al. 2009).

The oral cavity has a very unique environment and microorganisms and pathogens have easy access to it and the rest of the body through epithelium and the gastrointestinal tract (Dale and Fredericks 2005). Despite the high microbial load of the oral cavity that can potentially be disease forming, abrasions, cuts and minor surgical procedures rarely lead to infection. This indicates the highly effective host-defence mechanisms that exist and are active (Zasloff 2002). Oral epithelial cells, salivary glands and neutrophils secrete at least forty five identifiable antimicrobial gene products that are found in saliva. Saliva acts as a potent line of defense owing to its antibacterial, antioxidant and antifungal properties along with the oral mucosa, which plays a role as an important barrier (Amerongen and Veerman 2002, Yoshio, Lagercrantz et al. 2004). The most common AMPs that express in the oral cavity are listed in Table 2. Subsets of these AMPS are also expressed in the crevicular fluid and are more concentrated than in saliva (Alves and Olivia Pereira 2014, Ashby, Petkova et al. 2014). In addition to their role played as antimicrobials, AMPS also serve as effective biological molecules in immune activation, inflammation and wound healing (Yang, Biragyn et al. 2002, Koczulla and Bals 2003, Yang, Biragyn et al. 2004) and are being extensively researched upon for clinical applications (Koczulla and Bals 2003, Dale, Tao et al. 2006, Meyer and Harder 2007, Kang, Park et al. 2014, Vale, Aguiar et al. 2014).

2. Mechanisms of action

Many studies have previously researched and reported the mechanisms of action of AMPs against microorganisms (Vos, Kuipers et al. 1995, Gennaro, Zanetti et al. 2002, Ganz 2003, Brogden 2005, Dale, Tao et al. 2006, Gorr 2009, Melo and Castanho 2012, Tomasinsig, Skerlavaj et al. 2012, Haney, Petersen et al. 2013, Wang 2014). However, the mechanisms most widely accepted are the barrel-stave model, carpet model, and toroidal model for killing organisms. In *barrel-stave model*, peptides position themselves for binding on the cell membranes, this leads to peptide aggregation and conversion to a bilayer membrane. So in this way the hydrophobic peptides align with the lipid core and hydrophilic peptides form an access pore in the interior part of membrane (Figure 1.a). The *carpet model* is described as a disruption of the membrane by binding of peptides to the outer surface (phospholipids) of cell membrane and forming a prolonged layer or carpet (Figure 1.b). In the *toroidal model*, attached peptides start aggregation and force the lipid monolayer to bend incessantly through the pores. In this way the core is lined by both the inserted peptides and the lipid head groups (Figure 1.c) (Epand and Vogel 1999, Bocchinfuso, Palleschi et al. 2009). Types and role of antimicrobial peptides have been discussed here.

3. Types of oral antimicrobial peptides

3.1. Defensins

Defensins are short, cationic, low molecular weight (~4-5 kDa) peptides with ~6-8 cysteine residues which form 3-4 intramolecular disulfide bonds (White, Wimley et al. 1995). Defensins are extensively studied due to their wide expression in human body and the capability to kill all kind of gram-positive and negative bacteria, fungi and as well as viruses such as herpes simplex (Ganz 2003, Wang, Owen et al. 2004, Diamond and Ryan 2011, Wang 2014). Human defensins are classified as α-, β- and θ- on the basis of their length,

location, position of cysteine and folding of peptide chains (Abiko, Saitoh et al. 2007, Greer, Zenobia et al. 2013).

Mature α-defensin family have been isolated from human neutrophils as hNP-1, hNP-2, hNP-3 and hNP-4 (Selsted, Harwig et al. 1985). These neutrophils are nearly identical in amino acid sequences but the N-terminus of hNP-1 end with alanine (Ala) and aspartate (Asp) for hNP-3 (Figure 2). These changes affect defensin antimicrobial spectrum as already reported by *Ganz.et.al.* (Ganz, Selsted et al. 1985). The hNP-3 is less active than hNP-1 or hNP-3 in destroying *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli* (Ganz, Selsted et al. 1985). hNP-4 has been researched and identified by *Griffith et al.* by chromatographic methods, as 33 amino acid sequences expressed in neutrophils with activity against *E.coli*, *Streptococcus faecalis* and *Candida albicans* (Wilde, Griffith et al. 1989). The last two family members of α-human neutrophils peptides (hNP-5 and hNP-6) are present in the enteric system and do not express in the oral cavity (Gomes Pde and Fernandes 2010). In a healthy human, hNP-1 to 3 is most abundantly present in saliva (around 99 %). The levels of hNP-4 are roughly 100 folds lower (Gabay, Scott et al. 1989, Gomes Pde and Fernandes 2010). The concentration of hNP-1 is higher in saliva of patients with oral diseases such as lichen planus, leukoplakia and squamous cell carcinoma) in contrast to healthy individuals (Dunsche, Açil et al. 2001). The level of hNP-1, -2 and -3 has been shown to be reduced in edentulous patients due to the absence of gingival crevices (Fanali, Inzitari et al. 2007). *Dale et al.* have reported low salivary levels of α-defensins (hNP-1, -2 and -3) in patients having dental caries and suggested that these are biological factors that can be used for caries risk assessment in general population (Dale, Tao et al. 2006).

The β-defensins family contain six members (hBD-1-6), and principally they are all expressed in epithelial cells that cover several tissues and organs including the skin, mucosal surfaces of oral cavity, respiratory tract, gastrointestinal tract, genitourinary tract, and kidney

(Gorr 2011). The molecular structure of β—defensins is represented in Figure 2. Research has proved that only hBD-1, hBD-2, and hBD-3 are expressed in the oral cavity (gingival epithelia, tongue, palate and buccal mucosae, salivary glands/ducts and saliva) (Dale and Krisanaprakornkit 2001). Human Beta defensins -1 and -2 localized within the suprabasal layer of normal gingiva and hBD-3 peptide is expressed in undifferentiated epithelial cells within the basal layer (Pisano, Cabras et al. 2005). It has been suggested that hBD-1 is continuously expressed and plays a role in the impediment of normal flora from becoming opportunistic. Whereas the hBD-2 and -3 are inducible in response to bacterial lipopolysaccharides (LPS), proinflammatory mediators (Interleukins[IL-1β], tumor necrosis factors [TNF-α], interferons [IFN-γ]) and are more effective against almost all pathogens (Krisanaprakornkit, Weinberg et al. 1998). These peptides are in low concentration in the gingival crevicular fluid. Immunohistochemistry has been carried out in tissues sample from radicular cyst, lichen planus, leukoplakia and candida leukoplakia suggesting that hBD-2 is forcefully induced by lichen-planus related inflammation and play role in protecting candida albicans (Abiko, Jinbu et al. 2002). *Zhao et al.* reported that the location of human genes for α-defensins and β-defensins are adjacent to loci on chromosome 8p22-p23 (Liu, Zhao et al. 1997).

3.2. Histatins

Histatins are a family of salivary proteins with low molecular weight cationic peptides synthesized by the parotid and submandibular salivary ducts cells at around 50-425 µg/ml in healthy adults (de Sousa-Pereira, Amado et al. 2013). They are 7 to 38 amino acids residues in length with at least 12 histidine residues, hence called as *histidine rich proteins*. Histatins are predominantly antifungal and comprise of three main members (His-1, His-3 and His-5) with others members being generated from the proteolytic cleavage of these (Table 3) (MacKay, Pollock et al. 1984, Troxler, Offner et al. 1990). Along with the capability of

inhibiting the growth of *Candida* species, they have other functions like regulating oral haemostasis and bonding of metal ions in saliva (Bercier, Al-Hashimi et al. 1999, Oudhoff, van den Keijbus et al. 2009). Histatins have high affinity for enamel surfaces and play a role in the formation of acquired enamel pellicle (Richardson, Johnsson et al. 1993). Their antifungal mechanism has a few phases; bonding to the specific membrane, transport through membrane, inhibition of mitochondrial respiration by forming reactive oxygen species, entering the cell by mobilisation of ions (K^+, Mg^{2+}) and causing cell death (Xu, Levitz et al. 1991).

Oral candidiasis is a common infection in the human oral cavity associated with trauma or in immunocompromised patients due to low salivary flow (Sjorgren's syndrome). In these situations, histatins play an active positive role. *In-vitro*, Hst-5 has been shown to inhibit *Candida* species (*Candida albicans, Candida glabrata, Candida krusei, and Cryptococcus neoformans*) at physiological concentration (15-30 μM) (Raj, Edgerton et al. 1990). Another study demonstrated that Hst M (middle portion of Hst-3) has the same candida-cidal activity as the full length molecule and this indicates the potential future use of short length antifungal peptides for oral ointments (Raj, Edgerton et al. 1990). Common cause of biofilm in dental prosthesis is by colonization of *Candida* and Hst-5 has showed potent limiting effect on biofilm in comparison to chlorhexidene (Pusateri, Monaco et al. 2009). A promising antimicrobial peptide appears to be the histatin 5 12-mer P113 (Demegen) which works as a mouth rinse for oral candidiasis in patients with human immuno deficiency virus HIV (Gorr 2009, Gorr 2011).

3.3. Cathelicidins (LL- 37)

Cathelicidins (LL37) are AMPs from the family of α-helical peptides without cysteine and located at the carboxyl terminus of a 15-18 kDa highly conserved cathepsin-L-inhibitor (cathelin)-like domain (Lehrer and Ganz 2002, Kosciuczuk, Lisowski et al. 2012). Cathelicidins only have one delegate in humans in the oral cavity and respiratory tract) which is known as human cationic antimicrobial peptide (hCAP18) (Murakami, Ohtake et al. 2002, Tecle, Tripathi et al. 2010). They are synthesized and stored in cells as 2 -domain proteins and when required are split by proteases to produce a cathelin protein and an antimicrobial peptide. They derive their name from the first two residues at the N-terminus (**L**eucine, **L**eucine) and contain 37 amino acids (Zanetti, Gennaro et al. 2002). LL37/hCAP18 has the function of stimulation of monocytes, neutrophils, mast cells and T-cells. Various studies have demonstrated the capability of LL37/hCAP18 as a potent antimicrobial against many gram-negative and positive bacteria, fungi, viruses and parasites (Tanaka, Miyasaki et al. 2000, Isogai, Isogai et al. 2003, López-García, Lee et al. 2005). LL37/hCAP18 neutralize bacteria very quickly by forming ionic channels in the cell membranes of the microorganisms and by ability to bind LPS of bacterial membranes (Zanetti, Gennaro et al. 2002). *Turner, Cho et al.* reported minimal inhibitory concentration (MIC) of LL37/hCAP18 range of less than 10µg/ml against microorganisms (Turner, Cho et al. 1998). Another study demonstrated the stronger killing action action of LL37/hCAP18 derived synthetic peptides against *Streptococcus sanguis* (isolated from behcet's disease) (Isogai, Hirata et al. 2003). In addition, *Ouhara et al.* chemically synthesized human b-defensin-1 (hBD1), hBD2, hBD3 and LL37 (CAP18) for their antimicrobial activity against oral bacteria (*Streptococcus mutans*, S.sanguinis, *S. Salivarus* and *S. mitis*) and demonstrated the high activity of LL37 against these pathogens (Ouhara, Komatsuzawa et al. 2005).

3.4. Adrenomedullin

Adrenomedullin is a cationic amphipathic peptide with one disulphide bond. It is a proteolytically processed 185 amino acid protein initially that is C-terminally amidated to ~~produce~~ create the mature 52 amino acid adrenomedullin (Gorr 2009). This AMP is present in the gingival crevicular fluid and saliva. Although adrenomedullin is in both glandular and whole saliva, it is in large concentrations in whole saliva (Gorr 2009). This suggests that the oral epithelial cells donate to the salivary expression of adrenomedullin (Kapas, Pahal et al. 2004). It has been observed that the quantity of adrenomedullin is almost double in periodontaly compromised areas than in healthy areas (Lundy, O'Hare et al. 2006).

3.5. Statherin

Statherin is a 5.4 kDa peptide belonging to the histatin/statherin family. It is believed that statherin and a basic histidine-rich peptide might have developed from a common ancestral gene (Dickinson, Ridall et al. 1987). Antimicrobial properties are observed in C-terminal peptide of the statherin (Kochanska, Kedzia et al. 2000). Statherin is found in saliva (Vitorino, Lobo et al. 2004, Wilmarth, Riviere et al. 2004, Denny, Hagen et al. 2008) and the gingival crevicular fluid (Pisano, Cabras et al. 2005). This AMP is secreted by the submandibular and the parotid glands and hinders the growth of anaerobic bacteria isolated from the oral cavity (Vitorino, Lobo et al. 2004, Wilmarth, Riviere et al. 2004, Denny, Hagen et al. 2008). Statherin also restrains the crystallization of calcium phosphate and hence may have a protective role against plaque formation (Wilmarth, Riviere et al. 2004, Denny, Hagen et al. 2008). The proteomic analysis of saliva acquired from patients with high and low numbers for bacterial adhesion and agglutination has revealed the potential of statherin to be utilized as a biomarker for infections in oral cavity (Rudney, Staikov et al. 2009).

3.6. C-C motif chemokine 28

This is a 128-amino acid peptide, which is principally expressed in a variety of epithelial cells, including salivary glands, and is observed in saliva (Denny, Hagen et al. 2008). The C-C motif chemokine 28 acts both as a broad-spectral antimicrobial agent and also as a chemokine (Gorr 2009). A C-terminal 28 amino peptide has similarities with histatin 5 and this peptide is salt sensitive, and increases the permeability of cell membrane, as has been noted for other cationic AMPS (Hieshima, Ohtani et al. 2003).

3.7. Azurocidin

Human saliva proteomic analysis helped in the identification of azurocidin, which is a 37 kDa cationic antimicrobial protein expressed in azurophil granules of neutrophils 1(264,55). Azurocidin is a 251- amino acid protein has strong antibacterial properties towards gram-negative bacteria due to having strong affinity for lipopolysaccharide (Gorr 2009, Dhaifalah, Andrys et al. 2014). The two cystiene residues in positions 52 and 68 are thought to be essential for the antibacterial activity (Soehnlein and Lindbom 2009).

3.8. Neuropeptides

Gingival crevicular fluid contains the neuropeptides, calcitonin gene related peptide and substance P (Awawdeh, Lundy et al. 2002). In addition to these peptides, the neuropeptide Y and vasoactive intestinal peptide are also expressed and present in salivary fluids (Dawidson, Blom et al. 1997). However, their antimicrobial role is extremely limited since their concentrations varying from 2-45 pg/ml are lower by several orders of magnitude than the minimum inhibitory concentrations required to be effective against Candida albicans and bacteria (El Karim, Linden et al. 2008).

3.9. Role of AMPs in oral diseases

The exposure of gingival epithelial cells with bacteria related to periodontitis results in the production of β-defensins and LL-37 (Gorr 2009). Around twenty genetic disorders connected with periodontal disease have been identified to date (Hart and Atkinson 2007). Some of these disorders are associated with alterations in the AMP expression, which potentially increases the susceptibility to bacterial infections (Gorr 2009). It has been shown that conditions of sever congenital neutropenia (Marbus Kostman disease) are associated with severe irreversible periodontitis (Putsep, Carlsson et al. 2002). These patients have insufficient LL-37 in neutrophils, saliva and plasma. Also the α-defensins are markedly reduced (to about 30% of normal) while the lactoferin content in plasma remains normal (Putsep, Carlsson et al. 2002). Individuals suffering from Marbus Kostman when treated with granulocyte–colony stimulating factor demonstrate regular neutrophil count but still lack LL-37 and continue to suffer from advanced periodontal disease (Carlsson, Thilander et al. 1967, Putsep, Carlsson et al. 2002). It has been observed that bone marrow transplantation in a patient resulted in the restoration of both neutrophils and LL-37 to normal levels. While this proved that LL-37 is related to periodontal disease, normal levels were not enough to prevent or restore the periodontal disease alone (Bachrach, Chaushu et al. 2006, Gorr 2009). Periodontal disease is also common in children with Down's Syndrome (Trisomy 21) (Orner 1976). Mucin -7 and lactoferrin are other AMPs that are associated with periodontal disease. In A. actinomycetemcomitans-associated periodontitis, the levels of mucin -7 are decreased three fold when compared with disease free patients (Groenink, Walgreen-Weterings et al. 1999). Lactoferrin levels are shown to be within normal ranges, but the protein is iron saturated, indicating a reduction in the antimicrobial properties in patients with periodontitis (Groenink, Walgreen-Weterings et al. 1999).

Other oral diseases and infections have also exhibited relations to the levels of expression of AMPs. Low levels of variety of AMPs, including lactoferrin and β-defensins 1 and 2 are associated with oral candidiasis (Tanida, Okamoto et al. 2003). Remarkable variations in susceptibility to AMPs hBD3 and LL-37 have been noted between different species of oral bacteria and differing strains of the same species (Ji, Hyun et al. 2007). A good example of this is the Streptococcus Gordonii M5 that is weakly susceptible to both AMP hBD3 and LL-37, while Streptococcus. Gordonii 10558 is highly susceptible. P. Gingivalis 33277, by contrast, is less susceptible to LL-37 but greatly susceptible to death by hBD3 (Ji, Hyun et al. 2007). Haim–Munk syndrome and the Papillon–Lefe`vre syndrome are induced by allelic mutations of the cathepsin C gene, CTSC 1 and identified by severe periodontitis and palmoplantar keratoderma (Hart, Hart et al. 2000). Although, patients with Papillon–Lefe`vre syndrome express normal levels of the cathelicidin precursor, very little is processed to the mature LL-37 peptide. Similar to Morbus Kostman, it is lplausable that the decreased levels of LL-37 results in occurrence of periodontitis in patients with Papillon–Lefe`vre syndrome (de Haar, Hiemstra et al. 2006).

The interrelation of AMPs expression levels and occurrence of caries has been difficult to establish. Development of caries in children has been linked with the low-level expression of α-defensins (human neutrophil peptides 1–3) (Tao, Jurevic et al. 2005). However, due to the fact that caries is observed at broad variation in α-defensin expression levels, it cannot be definitely established whether α-defensin expression is accurately predictive of development of future caries (Dale, Tao et al. 2006). Also, salivary peroxidase and lactoferrin have not shown correlation with occurrence of caries in clinical studies carried out in children (Kirstila, Hakkinen et al. 1998) and adults (Grahn, Tenovuo et al. 1988). The wide variety and range of AMP expression levels between study subjects is possibly one of the strong reasons for the complication in relating single point analysis of AMPs with oral disease

(Tenovuo, Grahn et al. 1987). It is already known that salivary peptide levels between patients can differ about 100-fold (levels normalized to total salivary protein (Tao, Jurevic et al. 2005). This makes it very challenging to express exact or normal values for individual AMPs. A multiplex investigative and analytical approach towards antimicrobial protein expression in healthy and diseased individuals with the aim to recognize AMP signatures would potentially result in higher predictive/diagnostic power.

4. Conclusions

A wide range of AMPs with miscellaneous functions have been discovered in the oral tissues and secretions. The protective role played by these peptides against microbes entering the oral cavity results in effective fight against infections. The interest in the potential use of AMPs as a therapeutic regimen is due to their wide range of efficacy and low rates of induced resistance owing to the co-evolution of pathogens and the host AMPs. After reviewing the literature we can conclude that these AMPs have promising potential to be used against oral microbes in order control their growth and biofilm formation. There are many challenges that need to be overcome in order to design and synthesize AMPs that have the ability to withstand the unique and harsh oral environment. AMPs are expected in the future to be used as models for designing effective oral microbial antibiotics.

Conflict of interest

None

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Figure Legends

Figure 1 Illustration representing model of antimicrobial peptides for killing microorganisms. (a) Barrel-stave model, (b) carpet model, (c) toroidal model.

Figure 1 Molecular structure of human α-defensins with their cysteine consensus.

Figure 2 Molecular structures of β- defensins.

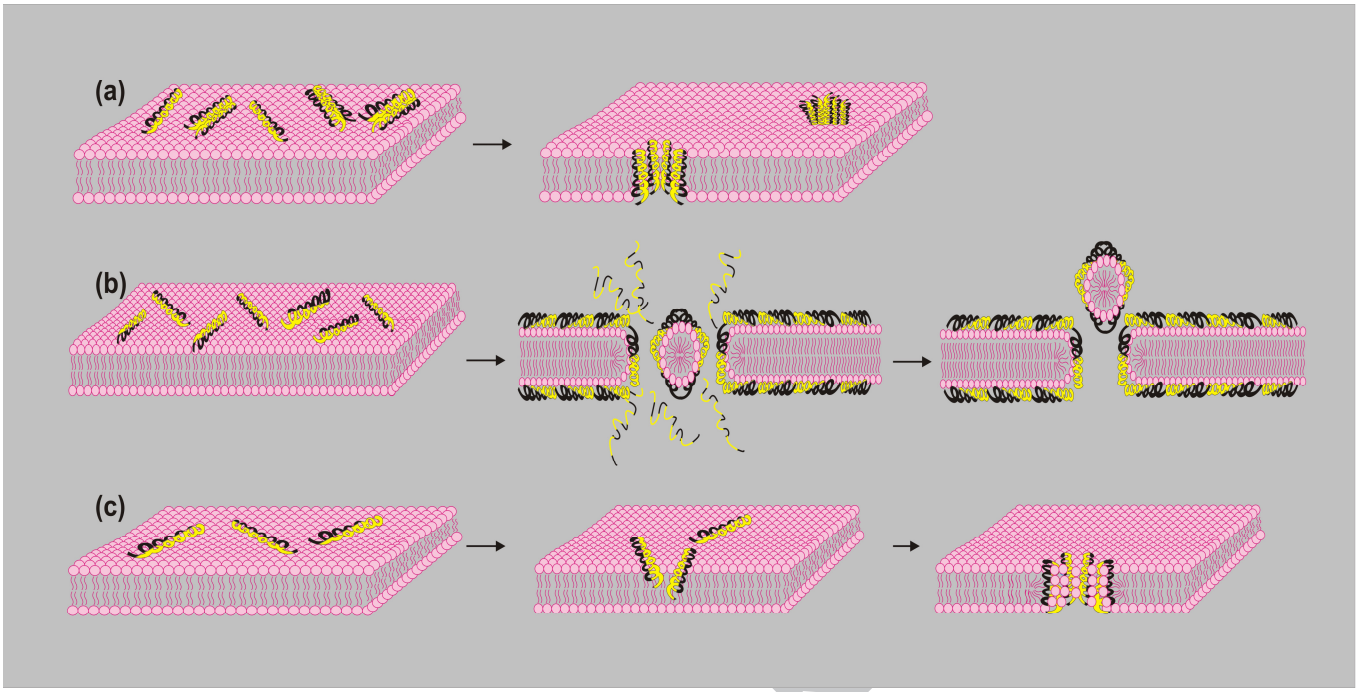

Figure 1 Illustration representing model of antimicrobial peptides for killing microorganisms. (a) Barrel-stave model, (b) carpet model, (c) toroidal model.

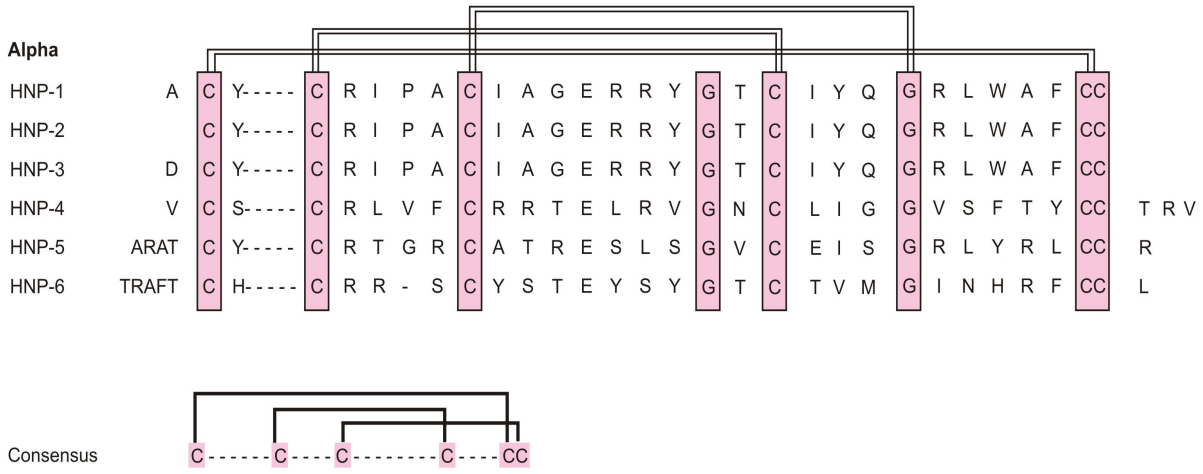

Figure 3 Molecular structure of human α-defensins with their cysteine consensus.

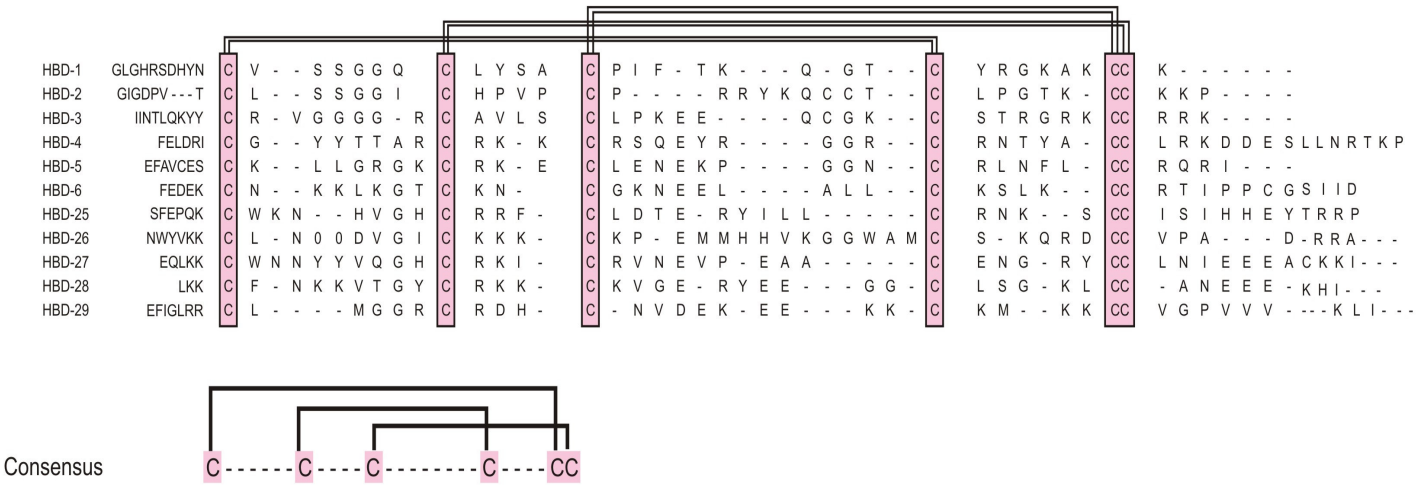

Figure 4 Molecular structures of β- defensins.

Table 1 Representation of Antimicrobial peptides classification on different basis.

Classes	Comments
Anionic peptides	They are small, rich in glutamic acids and aspartic acids, present in human, cattle and sheep.
Linear cationic α-helical peptides	They are short of cysteine and short peptides .e.g. LL37 from human.
Cationic peptides enriched for specific amino acids	They are proline rich peptides e.g. abaecin from honey bees.
Anionic and cationic peptides (contain cysteine and disulfide bonds)	They contain cysteins with one or more disulfide bonds e.g. protegrin from pigs, tachyplesins from horse crabs and α – β- defensins from humans, cattle, mice and pigs.
Anionic and cationic peptides fragments of larger proteins	They are similar to others AMPs but their role in innate immunity is not yet clear .e.g. lectoferricin from Lactoferrin and casocidin-I from human casein.

Table 2 Complete list of human oral antimicrobial peptides from Antimicrobial Peptide Database (APD)

Antimicrobial peptides	Year	Site of expression
α- Defensins (HNP-1)	1985	Neutrophils (azurophilic granules), gingival crevicular fluid and bone marrow
α- Defensins (HNP-2)	1985	Neutrophils (azurophilic granules), gingival crevicular fluid and bone marrow
α- Defensins (HNP-3)	1985	Neutrophils (azurophilic granules), gingival crevicular fluid and bone marrow
α- Defensins (HNP-4)	1989	Neutrophils
β- Defensins (hBD-1)	1995	Suprabasal layer of stratified epithelium and saliva
β- Defensins (hBD-2)	1997	Gingival epithelium and saliva
β- Defensins (hBD-3)	2001	Skin and salivary gland
Histatin-1	1988	Saliva (parotid and submandibular)
Histatin-3	1988	Saliva (parotid and submandibular)
Histatin-5	1988	Saliva (parotid and submandibular)
Adrenomedullin	1993	Epithelium
Cathelicidins (LL-37)	1995	Neutrophils, inflamed epithelia, submandibular glands and saliva

(http://aps.unmc.edu/AP/)

Table 3 Histatin Family with their proteolytic fragments.

Natural Histatins Present In Saliva	Sequences
Histatin 1	DSpHEKRHHGYRRKFHEKHHSHREFPFYGDYGSNYLYDN
Histatin 3	DSHAKRHHGYKRKFHEKHHSHRGYRSNYLYDN
Histatin 5	DSHAKRHHGYKRKFHEKHHSHRGY
	Proteolytic fragments in saliva
Histatin 2	RKFHEKHHSHREFPFYGDYGSNYLYDN
Histatin 4	KFHEKHHSHRGYRSNYLYDN
Histatin 6	DSHAKRHHGYKRKFHEKHHSHRGYR
Histatin 7	RKFHEKHHSHRGY
Histatin 8	KFHEKHHSHRGY
Histatin 9	RKFHEKHHSHRGYR
Histatin 10	KFHEKHHSHRGYR
Histatin 11	KRHHGYKR
Histatin 12	KRHHGYK